9/18/78

SUBJECT: Addendum of 6/30/78 and 8/17/78 to PP No. 7F1913 proposing a tolerance of 0.1 ppm for the herbicide metolachlor and its metabolites in or on soybeans and 0.02 ppm in eggs, milk, and the meat, fat of cattle, goats, hogs, horses, poultry and sheep.

FROM: Laurence D. Chitlik, Toxicologist
Toxicology Branch, HED (TS-769)
TO: George LaRocca, Acting PM#23
PETITIONER: Ciba-Geigy Corporation

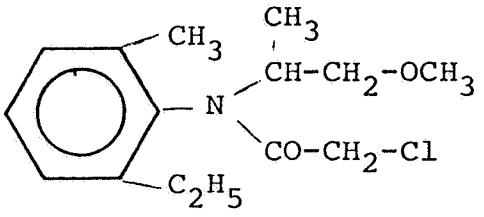
PESTICIDE PETITION: 7F1913

COMMON NAME: Metolachlor (formerly CGA-24705)

PRODUCT NAME: Dual(R) 6E

CHEMICAL NAME: 2-Chloro-N-(2-ethyl-6-methylphenyl)-N-(2-methoxy-1-methylethyl) acetamide

STRUCTURAL FORMULA:



PROPOSED TOLERANCE: (1) 0.1 ppm in or on soybeans
(2) 0.02 ppm in meat, milk & eggs

EXISTING TOLERANCES: (1) Temporary tolerance at 0.1 ppm and forage and hay at 1.25 ppm.

(2) 0.1 ppm corn grain

RELATED PETITIONS: 5G1553, 5F1606, 6G1708

NOTE: Refer to earlier review of Substantive Amendment to PP No. 7F1913, L.D. Chitlik, 5/3/78.

This memo covers Ciba-Geigy Amendments of 6/30/78 and 8/17/78.

BACKGROUND: Note pg. 3 of L.D. Chitlik review of 5/3/78, of Substantive Amendment to PP No. 7F1913. The following has evolved since that review.

The memo of D.L. Ritter, 8/23/78, raised the question as to whether the monochloroacetyl moiety (MCA) may theoretically be present in food as a residue of Metolachlor and that the analytical method would not detect this compound. Monochloroacetic acid is considered to be an adulterant when present in food at detectable levels of 10 ppb or more (21 CFR 189.155(b)). TOX deferred to RCB on this question. RCB, in the memo of D. Reed & W. Boodee, indicated that there are no data directly ruling out the presence of MCA, but available metabolism data & rational theoretical predictions all refute the postulation that MCA would be formed. Furthermore, they indicated that there is no evidence which indicates that CGA-37913 is directly formed (allowing release of MCA). but that if such a pathway exists, it would not be expected to lead to detectable levels of MCA where the major residues of metolachlor are in the 0.1 ppm range. RCB also concluded that (1) no additional data is necessary at this time and (2) if future uses of metolachlor are proposed, which lead to "high" residues on human food items, more data (a radiolabeled metabolism study, ^{14}C in the carbonyl position, on the subject crop) will be required.

RECOMMENDATIONS:

Toxicology data submitted in the addendums of 6/30/78 and 8/17/78 to PP No. 7F1913 (proposing a tolerance for the herbicide metolachlor and its metabolites at 0.1 ppm in or on soybeans and 0.02 ppm in eggs, milk and the meat, fat of cattle, goats, hogs, horses, poultry and sheep) are still insufficient for a human health hazard assessment.

The following deficiencies are noted:

(1) Both 90-Day rat and dog feeding studies are classified as invalid, because slides were not read by a pathologist. If these tissues are histopathologically examined by a pathologist, these studies may be re-classified.

(2) The tissues from the high dose level in the rat 90-day feeding study (Oncins Research & Breeding Center, Report IC-DREB-R 740120, 3/1/74) Group III, 1000 ppm for 10 weeks followed by 2000 ppm for weeks 11 through 13, (males 321-330 and females 351-360) must be examined and results submitted.

(3) NUMEROUS problems have been found in the mouse oncogenicity study (IBT No. 622-07925 (8532-07925) 12/15/77). Although none of the individual problems noted would be enough to invalidate this study, all of them combined may have impact on the integrity of conclusions drawn from this study. These problems relate to (1) Not following the protocol (2) Not recording and/or reporting of data (3) Poor animal husbandry & (4) Unscheduled sacrifices (recorded as moribunds). Although some questions have been clarified in addendums submitted (including a revised report of this study) others remain which cannot (or have not) been answered (i.e.-large no of "missing animals" etc).

Even with all the stresses on the animals that have been determined (Diseases, mite infestations, lack of food & water(?)) as well as unavailable data and a large number of "missing" animals, the pathology data still indicates that metolachlor is not carcinogenic when fed at levels of 30, 1000 and 3000 ppm. Some small problems have been noted in the pathology data, but it clearly shows no carcinogenic potential.

Since problems are so widespread within this IBT study the whole integrity of the study must really be questioned and for this reason it is recommended that a second opinion be obtained to ascertain its acceptability as a "valid" study, although I find it is acceptable. Audit of the data should also be considered. (See data review attached)

NOTE: The above findings/recommendations need not be considered at this time because the revised report was not signed and must therefore be classified as INVALID data until this problem is rectified.

(4) A second oncogenic study must be submitted.

(5) A chronic feeding study must be submitted. Conduct of the rat chronic feeding study was completed a number of months ago, but the report has not been completed. Ciba-Geigy has explained that due to IBT internal problems, there have been great delays.

In summary, as in the previous review of 5/3/78, although available data indicate metolachlor to have a relatively low order of toxicity, data submitted in the addendums of 6/30/78 and 8/17/78, are still insufficient for a favorable recommendation.

9-18-78

George F. Whitmire
9/18/78

3. Addendum of 6/30/78 to Mouse Oncogenicity Study (Revised Report) CDL: 097169 and 097170 Gesme, J.; Albanese e.; Marias, A.J.; Arces, R.J. (December 15, 1977) Carcinogenicity Study with CGA-24705 Technical in Albino Mice: IBT No. 622-07925 (8532-07925). Received January 18, 1978 under 7F1913. Unpublished report prepared by Industrial Bio-Test Laboratories, Inc. for CIBA-GEIGY Corp., Greensboro, N.C.: CDL: 096719 and 096720

REVIEWED BY: Laurence D. Chitlik, Toxicologist
Toxicology Branch, HED (TS-769)

DATE OF REVIEW: September 12, 1978

The revised report indicated a number of differences from the original submission. The following is a list of these differences:

(1) II SUMMARY pg. 2

Included a discussion of reduction in body weights after month 11 which was attributed to "Change in feed containers and a reduction in dietary fat content."

The statement was also included that observations, "in most cases", were evident in controls and test groups.
NOTE: The original report stated no "unusual behavioral reactions occurred during the investigation."

(2) III Procedure

A. Animals were assigned "arbitrarily" to control and test groups rather than "randomly" as the original report states.

B. Animals were identified by ear punch for the first 16 months and then identified by Monel metal ear tags from Month 16 through termination. In the original report it is stated that animals were identified with numbered metal ear tags only.

C. Purina Mouse Chow (10% fat) was used for the first 48 weeks and then was replaced with Ralston-Purina Rat Chow (not less than 4% fat) from week 49 to termination.

The original report states that only Ralston-Purina Rat Chow was used in the study and does not explain the diet change.

D. Stainless steel gravity fed feeders replaced large mouth glass food jars after Month 12 and 13 respectively, for the males and females tested. "Because of improper dispension of the diet, the feeders were modified slightly within two weeks of initial use."

No discussion of this change or the accompanying problem was included in the original report.

E. Mortality and reactions

"Observations for moribund animals and/or deaths were conducted twice daily (approx. 9 AM and 3 PM) during weekdays and only once per day on holidays and weekends".

Observations for abnormal reactions were recorded during the daily morbidity checks for the first four months, once per month during months 5-10, and twice per month during Months 11-20 (18 for males). The original report states simply, "Observations for abnormal reactions and/or deaths were conducted twice daily (approx. 9 AM and 3 PM).

NOTE: No observations were recorded until the fifth month (although a number of animals died during this 5 month period including four females which died on days 55 through 118). According to the report these were "natural deaths." (No tissues were taken from these animals although 2 morbidity checks were made daily. Of course it is possible that all 4 animals died on weekends.....allowing a proper interval for autolysis. This conclusion is obviously speculation, however, but results of the necropsy are not included in the pathology report and therefore no conclusions can be drawn.....

See review of 5/3/78, L. Chitlik, PP #7F1913 for further discussion of this point.

Revised report has an observation section while the original report contained none at all. The incompleteness of the observations made during this study are quite evident from the tables submitted in the revised report.

F. The animal water supply was treated with 10-15 ppm chlorine during weeks 77-87 of the study. The revised report also indicates this was a preventative measure.

The original report made no mention of this. A question pertaining to the "preventative nature" of this treatment was addressed to Dr. Steven on 7/20/78, and answers provided in the addendum of 8/17/78 indicate the treatment was an attempt to correct a "Pseudomonas problem" which to this reviewer relates directly to observation of skin, eye, and ear infections noted in the observation section of the revised report of 6/30/78. There is, however, no discussion within either of the two reports associating the noted observations to this water problem.

NOTE: Further discussion within the review of the 8/17/78 addendum to this petition.

(3) Results Section of Report

A. The revised report indicates the (1) Change in diet and (2) Change from food jars to stainless steel feeders, was responsible for reductions in body weight in control and test groups after month 11.

The original report contains no discussion of any of this.

B. The original report states "No unusual behavioral reactions were observed during the investigation." The report did not include any daily observations. The revised report states that at approximately 8 months, 4 control males, 1 -I male, 5 T-II males and 1 T-III male developed skin lesions of the head and/or the cervical region. Scratching caused these lesions to spread to the eyes and ears and that this is believed to be the cause for blood observed in the ear canal of some mice later in the study. These animals were examined by a staff pathologist and diagnosed as ulcerative dermatitis. Skin scraping and tissue sections failed to reveal the cause. "An occasional mite" was noted in examination of animals from an adjacent study. It was concluded that this along with the "possible allergic nature of the skin lesions" was a probable cause.

These animals were sacrificed and classified in the report as moribund. The report states that "some" of the mice were near death.

Eye irritation and alopecia were attributed to old age (?) and not considered treatment related.

NOTE: Neither the original nor the revised version of the report discussed the "Pseudomonas problem" which also occurred during this study, and was noted in a later addendum (8/17/78).

Body tremors and general weakness were observed in the T-II and T-III females during the fourteenth month of testing (Day 419, 8:00-9:00 AM) and Not in other test groups or controls. After one hour, the affected animals appeared normal). This was not observed during any other time during the remainder of the study. The cause was not determined.

NOTE: Observations were recorded very infrequently and tremors MAY have occurred very frequently. Observations were not conducted at a frequency anywhere near what was specified in the original report.

Physical and behavioral observations were submitted as an addendum. The report concluded that the observed reactions were not treatment related.

The revised mouse oncogenicity study report is not signed by responsible personnel at the testing laboratory and it cannot therefore be used for regulatory purposes (at this time).

2. Addendum report of 6/30/78, to Dog 3-Month Feeding Study, Technical Metolachlor, The Oncins Research and Breeding Center, Report IC-DREB-R 740119, 1974, Received originally under PP No. 5G1553 with re-evaluation by T. Edwards.

REVIEWED BY: Laurence D. Chitlik, Toxicologist
Toxicology Branch, HED (TS-769)

DATE OF REVIEW: Sept. 12, 1978

This addendum contained a review of lung pathology by a second pathologist, A.F. Pelfrene, M.D. The following conclusions are noted:

1. With the exception of one dog, no associated inflammation was observed. Pulmonary infection was ruled out as a cause of lesions found in these lung tissues. NOTE: The original report stated "pulmonary lesions similar to those seen in some bacterial of virus infection" were noted!

2. No foreign body reaction was observed in the lungs of these animals nor have foreign particles been observed with a polarizing microscope.

3. The lesions observed, including fibrinous exsudation, edema of alveolar walls, perivascular and alveolar haemorrhages and congestion are premortem in origin induced by the method of sacrifice.

4. Sub-pleural fibrosis (independently from any inflammation) is usually observed in dogs at this facility.

5. Lesions were equally distributed among all groups and are not compound related.

This reviewer concurs with this reading of lung tissues by the second pathologist. As in the rat 3 month feeding study addendum, this report was more precise with better description and a grading system.

Group III animals (500 ppm) showed no toxic manifestations except slight and not significant weight loss of the females of this group. The "NOEL" in this dog three month oral feeding study is 500 ppm.

In the review of E.L. Long, M.D., Pathologist, 3/14/78, PP #5G1553, 90-Day Rat Feeding study, Dr. Long discussed a number of shortcomings of the pathology data submitted.

Included in her review were several points of note:

(1) Some terminology is incorrect e.g. "Hemorrhagic alveolitis" should be simple "hemorrhage."

(2) Another possible reason suggested by Dr. Long for another finding was, "Over reading of the slides by an inexperienced pathologist."

(3) Dr. Long also noted that "Better descriptions of the lesions seen" should be obtained from the pathologist.

These points originally raised by Dr. Long, prompted the question as to whether Dr. Fouillet was indeed a pathologist. American Cyanamid was asked this question and the memos of Jack Norton, 9/8/78, A.F. Pelfrene, M.D., 8/21/78 and the Curriculum Vitae of Dr. Fouillet were received 9/11/78. They indicate clearly that Dr. Fouillet has a Doctorate in animal biology (Cytology and histology major) and is NOT a pathologist.

We therefore find that until readings are conducted by a pathologist, that this study, also read by Dr. Fouillet, is not acceptable for tolerance setting purposes.

DATA REVIEW:

Addendum of 6/30/78 for clarification/re-evaluation of the following studies:

1. Addendum report of 6/30/78 to Rat, 3-Month Feeding Study, Technical Metolachlor, The Oncins Research and Breeding Center, IC-DREB-R 740120, 3/1/74 Received originally under PP No. 5G1553 with re-evaluation, 1/25/78, in conjunction with PP #7F1913, 5/3/78.

REVIEWED BY: Laurence D. Chitlik, Toxicologist
Toxicology Branch, HED (TS-769)

DATE OF REVIEW: Sept. 12, 1978

Lung tissues were re-evaluated by a second pathologist, A.F. Pelfrene, M.D. Slides were bindly examined at random (without knowledge of treatment group assignment). Definitions of terminology were included to avoid the possibility of translation misinterpretation.

One question raised in the review of L. Chitlik, 1/25/78 and subsequently in the review of E.L. Long, 3/14/78, concerned the nature and cause of the "thickening of the alveolar walls." The definition given in this addendum report tends to clarify this significantly (the thickeness of the alveolar wall is increased by interstital edema and/or by "balloning" of parietal cells, reducing the air space of the alveoli) and eliminates any previous significance attached to this findings. This finding was noted in nearly all the lung tissues examined, including controls.

The re-review of the lung tissues by A.F. Pelfrene included a number of findings not noted in the original report. Generally, however differences were not of a significant nature. This report also was more precise since better description and a grading system was used. Dr. Pelfrene made the following conclusions:

1. The possibility of pulmonary infection was rejected since there was no associated inflammation (with several exceptions).

2. No foreign body reaction nor polarizing particle was observed in the parenchyma, hence no airbone contamination occurred.

3. The lesions noted are considred pre-mortem in origin (the animals were anesthetized with ether and then decapitated).

4. The lesions noted are not compound related.

The term "hemorrhagic alveolitis" is not used in the addendum by Dr. Pelfrene. Dr. Long noted, in her review of 3/14/78, that this use of "alveolitis" was incorrect.

Pelfrene defines this finding as interstitial haemorrhage where alveolar walls are filled and thickened by a considerable amount of blood. He also states that this is often associated with intra-alveolar haemorrhage (presence of large amounts of blood in the alveoli lumen). Additionally findings of firbrinous alveolitis (presence of exudates consisting of eosinophilic material (fibrin) mixed with poorly stained fluid in the air space of the alveoli) and Macrophagic alveolitis (presence of macrophages with a foamy cytoplasm in the air-space of the alveoli) were noted in this new report.

The report did not include examination of all animals of Group III (1000 ppm for 10 weeks followed by 2000 ppm for the last 3 weeks) including males 321-330 and females 351-360.

The Conclusion noted in the 1/25/78 review where the observed NEL was determined to be 1000 ppm remains the same. Questions pertaining to the "alveolar wall thickening" and "hemorrhagic alveolitis" have been resolved. The tissues from high dose animals (listed in the above paragraph) must still be examined.

In the review of E.L. Long, M.D., Pathogist, 3/14/78, PP #5G1553, 90-Day Rat Feeding study, Dr. Long discussed a number of shortcomings of the pathology data submitted.

Included in her review were several points of note:

(1) Some terminology is incorrect e.g. "Hemorrhagic alveolitis" should be simply "hemorrhagic."

(2) Another possible reason suggested by Dr. Long for another finding was, "Over reading of the slides by an inexperienced pathologist."

(3) Dr. Long also noted that "Better descriptions of the lesions seen" should be obtained from the pathologist.

These points originally raised by Dr. Long, prompted the question as to whether Dr. Fouillet was indeed a pathologist. American Cyanamid was asked this question and the memos of Jack Norton, 9/8/78, A.F. Pelfrene, M.D., 8/21/78 and the Curriculum Vitae of Dr. Fouillet were received 9/11/78. They indicate clearly that Dr. Fouillet has a Doctorate in animal biology (Cytology & histology major) and is Not a pathologist.

We therefore find that until readings are conducted by a pathologist, that this study, is not acceptable for tolerance setting purposes.

Rat Two Year Feeding Study, (Only Histopathology Report of lung findings) CGA 24705 Technical, Industrial Bio-Test Lab., Inc. IBT No. 8532-07926, June 12, 1978.

The histopathology findings were confined to lung tissue only. This lung tissue report was submitted to clarify lung pathology findings noted in earlier 90-day studies submitted by Ciba-Geigy. The following mortality data was also noted:

Males Group	Final Sacrifice	Mortalities & Moribund 0-12 Mon.	13-24 Mon.	Total	% Mort.
Control	22	4	33	59	61.6
30 ppm	14	2	44	60	76.6
300 ppm	20	5	35	60	66.6
1000 ppm	15	9	36	60	75.0
3000 ppm	17	4	37	58	68.3
Females					
Control	26	6	28	60	56.6
30 ppm	32	1	27	60	46.6
300 ppm	30	0	30	60	50.0
1000 ppm	31	0	29	60	48.3
3000 ppm	22	0	38	60	63.3

From the table above, under the column "Total" it is evident that 3 animals,

(1) control and (2) 3,000 ppm males were not accounted for in the tables submitted nor in the accompanying audit report by Ciba-Geigy. Mortalities were obviously higher among the males, but there appears to be no compound related effect on this parameter.

It should also be noted that approx 99% of the animals in this study had chronic murine pneumonia and it would not be appropriate to draw any further conclusions from this data until the completed study is submitted.

From the table above, under the column "Total" it is evident that 3 animals.

Addendum of 8/17/78 to Previously Submitted Toxicology Data (097269)

REVIEWED BY: Laurence D. Chitlik, Toxicologist
Toxicology Branch/HED (TS-769)

DATE OF REVIEW: Sept. 12. 1978

On July 20, 1978 Mr. Chitlik discussed with Dr. J.T. Stevens new questions related to the Ceiba-Geigy submission of 6/30/78, (addendum to EPA Reg. No. 100-583). On August 17, 1978 another addendum was submitted by Ceiba -Geigy in an effort to answer these questions. The following is a review of the submission of 8/17/78 (which attempted to answer 4 questions raised in response to the submission of 6/30/78):

(1) It was noted in the review of the audit report of the 2-year mouse oncogenicity study, that 37 animals of the four hundred on test were "missing".

Mr. Chitlik requested that Ciba-Geigy clarify this. If was further suggested that Ceiba-Geigy review the raw data to verify the individual animal numbers and the length of time the animals were on study.

In response Ceiba-Geigy referenced their submissions of 1/17/78 and 6/30/78 (both original and revised reports, the latter page references were incomplete and actually are the same as the original report, pages 106-121 and the accession no. of the original report is 096719. They also stated that the "original records" had been reviewed by Dr. Stevens and were found to be in agreement with the reports submitted.

It was also noted that this point was discussed with Dr. Orville Paynter by George Rolofson on 6/10/77, and by Dr. F. Kinoshita of IBT on 6/15/77. Dr. Paynter stressed that the number of animals on test at 18 months was, of course, the most important factor and would be given more weight.

According to this addendum, "escapes occurred when cages were jarred loose by attendants during the cleaning operations" and that when the problem was recognized, spring latches were installed on "many" of the cages.

A table indicated that escapes occurred in all groups in approximately equal numbers (4-7) with the exception of control females where no animals were lost. Escapes began 43 days into the study and continued to 531 days. In only one case did more than one female (housed 5 per cage) escape on the same date.

A statistical analysis was performed by Ceiba-Geigy in an attempt to show that for the purpose of an oncogenic evaluation, the number of escapes were not significant. This evaluation, however ignores the fact that ALL of these tissues were lost completely and that tumor formation also occurrs in animals that died before the terminal sacrifice. This evaluation is therefore of little or no real "unbiased" support for the contention made by Ceiba-Geigy.

(2) The question was alo raised whether the 10-15 ppm chlorine, added to the watering system, was completely preventative in nature or to correct some "problem" relating to the watering system (malfunction etc.)

As noted in the memo of A. Marias, 5/12/77, (EXHIBIT 1) there was a "Pseudomonas problem" which he had discussed with Dr. Ted Harris a number of times. A. Marias also indicated that "The water consumption may be reduced so we will have to watch the animals closely during the next few days."

In another memo from A.J. Marias, it was stated, "The animals are in poor health and the chlorinated water may add to their stress. We will continue to drain the racks several times weekly to maintain a fresh water supply to the mice.

The answer to the question is that there was a "problem" and that the adding of chlorine to the water supply was a corrective measure rather than preventative in nature. This is another example of poor data reporting by IBT. It should be noted that the original report didn't even indicate chlorine was added to the water supply at 10-15 ppm. The addendum submitted by Ceiba-Geigy very superfluously stated the values of chlorine to animals and mankind (which had nothing to do with the original question) in hopes of explaining why this situation would not compromise the integrity of their study.

(3) Another question raised related to whether animals were actually ear punched for the first 16 months and then ear tagged for the remainder of this study. Of particular interest in this question was the first five months when no body weights were recorded.

In response, IBT was unable to supply any documentation to verify when ear punching of group-housed females (5 per cage) took place! It appears that only cage cards identified individually housed males.

The only evidence available during the first 155 days of study which indicates any identification of females was for 4 dead and 2 missing animals which were assigned numbers! It is interesting to note that, (A) These four animals that were "Natural Death" (193, 261, 267, 285) during this period (115 days), had no tissues taken or examined and although the "Animal Disposition" table XVII indicates that gross examinations were made, none are presented in the report!

(B) No evidence of unique identification is provided for any live females (ie - no observations) for the first 5 months.

(C) "Individual identification strips" (for males & females?) were located for animals in the microfiche, but these were not submitted in this addendum.

(D) It appears that the "data trail" left by these animals, at least during the first 5 months, is impossible to verify because proper records, to be prepared at the beginning of such a study, & the data of the original animal identification, are not available. Furthermore, no daily observations were conducted during the first 5 months of this study (even though the original report indicates this was done twice daily) and so the chance of following at least some animals back during this period was eliminated.

(4) 2 year rat feeding study -(lung pathology only) Review of Addendum of 8/17/78, PP No. 7F1913.

Lung pathology of the 2-year rat feeding study was submitted 6/30/78 is hopes of clarifying questions raised in the 90-day rat and dog feeding studies. All males could not be accounted for in this submission (Lung pathology for 3 animals were accounted for in the original pathology sheets. They were too autolyzed to be examined (EXHIBIT 3).

Mr. Chitlik also noted the high incidence (nearly 100%) of chronic murine pneumonia found in these animals. In response Dr. Donovan Gordon IBTL Pathologist presented a statement (EXHIBIT 4) claiming that this would not preclude or compromise this study.

With respect to this lung pathology submission, evaluation of, or drawing conclusions from, this data without the submission of a completed study from Ceiba-Geigy, would not be appropriate at this time.

Page 8 of the addendum of 8/17/78 under the title "Points Made by Mr. Chitlik During July 20, 1978 Telephone Conversation"

A. Essentially this section attempted to clarify or explain the tremors, noted in T-II and T-III females noted 8-9 AM, day 419 (during the 14th month of testing).

Two possible explanations were given. The first suggested that low temperature (mid-January with very cold weather) was the cause. If this were the case, the tremors would not have been confined to two groups and outside weather should not have effected these animals anyway. The second explanation was "poor water pressure to the cage rack in question" which this reviewer is at a loss in understanding how this answers a question related to tremors in test animals!

It has also been the contention of Ceiba-Geigy that tremors confined to 2 groups of animal for one hour, on one day, of a 20 month study (even if caused by mix-up of diet from another study) would not compromise the oncogenic evaluation REGARDLESS OF CAUSE.

The basic flaw in their contention is that the tremors, as noted in the "Observations," occurred only at one time. Since there were long periods (5 months to 2 weeks) between animal observations, how valid is this contention? It therefore is impossible to state that this is an isolated incident and that it didn't occur much more often. Furthermore, if this were induced by a diet mix-up (a number of other oncogenic studies were run in the same room), this may have been quite common and rats MAY have gone for some time without CGA-24705 in their diet! Diet analyses were performed by Ceiba-Geigy only during the 19th & 20th months of the study which is after males were terminated.

B. The final point discussed in this addendum relates to the fact that the revised report was not signed and it is considered a draft.

As noted in the August 17, 1978 memo of Reto Engler, all unsigned reports will be declared invalid. The revised report (622-07925) must be signed by the responsible persons before this report can satify this data requirement.

R. E. W.
9/18/78